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ABSTRACT

A subject of the present invention is the use of anti-progestomimetic compounds for the manufacture of compositions intended for the synchronization of giving birth in breeding animals.

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PATENTS ACT 1964

COMPLETE SPECIFICATION

"NEW USE OF ANTI-PROGESTOMIMETIC COMPOUNDS IN BREEDING ANIMALS"

APPLICATION No. 727/91

SPECIFICATION FILED. 5/3/91

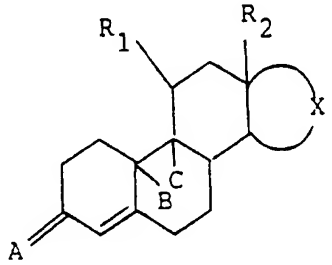
ROUSSEL-UCLAF, a French Body Corporate, of 35, Boulevard des Invalides, 75007 Paris, France

New use of anti-progestomimetic compounds in breeding animals.

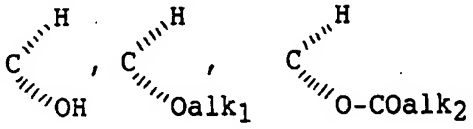
The present invention relates to a new use of anti-progestomimetic compounds in breeding animals.

A subject of the invention is the use of anti-progestomimetic compounds for the manufacture of compositions intended for the synchronization of giving birth in breeding animals.

More particularly a subject of the invention is the use, characterized in that the compounds endowed with anti-progestomimetic activity correspond to general formula (I):



(I)

in which R_1 represents a hydrocarbon radical containing 1 to 18 carbon atoms and optionally one or more identical or different heteroatoms, linked to the steroid nucleus by a carbon atom, R_2 represents a hydrocarbon radical containing 1 to 8 carbon atoms, X represents the remainder of a pentagonal or hexagonal ring optionally substituted and optionally carrying an unsaturation, the C=A group in position 3 represents a free or blocked oxo group in the form of the ketal, a  group, a C=NOH group, a $C=NOalk_3$ group or a CH_2 group, alk_1, alk_2 and alk_3 representing an alkyl radical containing 1 to 8 carbon atoms or an aralkyl group containing 7 to 15 carbon atoms and B and C together form a double bond or an epoxide bridge, as well as their addition salts with acids.

Notably a subject of the invention is the use, characterized in that the compounds endowed with anti-

progestomimetic activity correspond to general formula (I) in which R_1 r pr sents a hydrocarbon radical containing 1 to 18 carbon atoms containing at least one nitrogen, phosphorus or silicon atom linked to the steroid nucleus by a carbon atom.

R_2 represents preferably a saturated, linear or branched alkyl radical, containing 1 to 4 carbon atoms, for example, a methyl, ethyl, n-propyl or butyl radical.

When alk_1, alk_2 or alk_3 represents an alkyl radical, it is preferably the methyl, ethyl, n-propyl or isopropyl radical.

When alk_1, alk_2 or alk_3 represents an aralkyl radical, it is preferably a benzyl radical.

X represents preferably the remainder of an optionally substituted pentagonal ring.

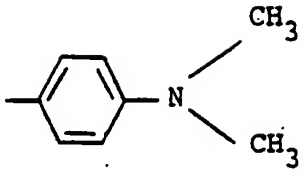
The compounds of formula (I) are known compounds which are described and claimed in the European Patent 0,057,115 and French Patents 2,566,779 and 2,625,505 where they are shown as endowed with different properties, pharmacological properties and notably an anti-progestomimetic activity.

Some products of formula (I) which are described and claimed in the French Patent Application 89 10648 filed on 8th August 1989 are not yet published; their preparation is given hereafter in the experimental part.

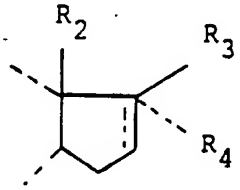
It has just been discovered that the compounds of formula (I) allowed a remarkable synchronization of giving birth in breeding animals as the results set out hereafter in the experimental part show.

After the injection of the product at a suitable dose, the products of formula (I) bring about birth within a time period of less than 36 hours, indeed of less than 24 hours.

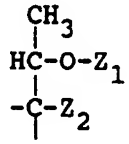
Among the preferred uses, there can be mentioned the use characterized in that in the product of formula (I), B and C together form a double bond, that where in the product of formula (I), R_2 represents a methyl radical, that where in the product of formula (I), the C=A group represents a $\overset{O}{\overset{\|}{C}}$ group, that where in the product of formula (I), R_1 represents a radical:



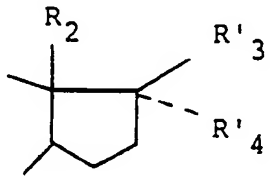
that where in the product of formula (I), X represents the remainder of a ring:



in which R_2 retains the same meaning as previously, R_3 and R_4, identical or different, represent either a hydrogen atom, or an OH, $Oalk_4$, $O\text{-}COalk_5$ radical, alk_4 and alk_5 representing an alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to 15 carbon atoms, or an alkenyl or alkynyl radical containing 2 to 8 carbon atoms, or an $-\overset{O}{\overset{\|}{C}}-CH_2OH$ radical, or a $-COCH_2OCOalk_6$ radical, in which alk_6 represents an optionally substituted alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to 15 carbon atoms, or a $CO\text{-}CO_2H$ radical, or a $CO\text{-}CO_2alk_7$ radical in which alk_7 represents an alkyl radical containing 1 to 8 carbon atoms, or a $-\overset{H}{\overset{|}{C}}=O$ radical, or a $-\overset{NHalk_8}{\overset{|}{C}}=O$ radical, in which alk_8 represents an alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to 15 carbon atoms, or a $-C\equiv N$ radical, or R_3 and R_4 together form a radical:



- in which Z_1 represents a hydrog n atom, an alkyl radical or an acyl radical containing 1 to 8 carbon atoms and Z_2 represents an alkyl radical containing 1 to 8 carbon atoms and notably that where X represents the remainder of a ring:



in which R_2 retains the same meaning as previously and R'_3 represents an OH radical, and R'_4 an alkynyl or alkenyl radical containing up to 4 carbon atoms.

Among the preferred forms of the invention, there can be mentioned the use where the anti-progestomimetic compound is 17beta-hydroxy-11beta-(4-dimethylaminophenyl)-17alpha-(prop-1-ynyl)-estra-4,9-dien-3-one (called hereafter product A) or also that where the anti-progestomimetic compound is (Z) 11beta-[4-(dimethylamino)-phenyl]-17beta-hydroxy-17alpha-(1-propenyl)-estra-4,9-dien-3-one or also 11beta-[4-(methylthio)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl butanedioate or one of its alkaline salts and notably its sodium salt or also 11beta-[4-(dimethylamino)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl butanedioate or one of its alkaline salts and notably its sodium salt.

The preparation of the latter two products mentioned last is shown hereafter in the experimental part.

More particularly a subject of the invention is the use, characterized in that the administration take place in a sow or cow or also a goat, ewe, mare.

The compositions are administered preferably by injection.

In a preferred method of use, the administration takes place by injection in the sow between the 109th and 114th day of gestation of 17beta-hydroxy-11beta-(4-dim thyl-aminophenyl)-17alpha-(prop-1-ynyl)-estra-4,9-dien-3-one at a dose of between 1 mg and 3 mg per kg of animal weight, for

exampl 2 mg/kg of animal weight.

The following xamples illustrate the invention with ut however limiting it.

PREPARATION 1 : Butanedioate of 11beta-[4-(dimethylamino)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl and sodium.

STAGE A : 11beta-[4-(dimethylamino)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl acid succinate.

The reaction medium is prepared by adding 2.15 g succinic anhydride, 2.2 cm^3 of triethylamine and 215 mg of 4-(dimethylamino) pyridine to a solution of 2.15 g of 11beta-[4-(dimethylamino)-phenyl]-17beta-hydroxy-17alpha-(1-propynyl)-estra-4,9-dien-3-one in 22 cm^3 of chloroform, then heated under reflux for 42 hours and 430 mg of 4-(dimethylamino) pyridine and 4.4 cm^3 of triethylamine are added. Reflux is continued for 26 hours and the solution is then poured into a water-ice mixture. After decanting the organic phase, it is washed then dried and the chloroform is distilled off to give a dry brown coloured extract. The aqueous phase is acidified with 0.5N hydrochloric acid then neutralized by addition of sodium acetate. Extraction is carried out again with ethyl acetate and the new organic phase is washed with water, dried and after distillation of the solvent a residue is produced which is reunited with the previous one. The product is purified on a silica column eluting with an ether-ethyl acetate (9-1) mixture with 3% acetic acid and recrystallized twice from an ether- methylene chloride mixture. 1.435 g of desired product is obtained. M.P. = approx. 165°C.
$[alpha]_D = +97^o$ (c = 0.8% in $CHCl_3$).
Rf = approx. 0.40 (thin layer chromatography, support: SiO_2, eluant: ether 9 - ethyl acetate 1 - acetic acid 3%).

STAGE B : Butanedioate of sodium and 11beta-[4-(dimethylamino)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl.

3 g of the product prepared as in stage A above and 94 cm^3 of ethanol are introduced into a flask provided with magnetic agitation and then a solution of 433 mg of sodium bicarbonate in 94 cm^3 of water is poured in. After agitating

for 30 minutes at ambi nt temp rature, ethanol is removed by azeotropy and the remaining solution is filtered on a millipore ^{R} membrane (0.45 microns) and lyophilized. 2.88 g of desired product is obtained.

$[\alpha]_D$ = +48.5 ± 1.5° (c = 1% in water).

Rf = 0.54 (thin layer chromatography, support : KC 18 Whatman ^{R}, eluant: methanol - 0.5 molar aqueous solution of ammonium acetate (80-20).

PREPARATION 2 : Butanedioate of sodium and 11beta-[4-(methylthio)-phenyl]-3-oxo-17alpha-(1-propynyl)- estra-4,9-dien-17beta-yl.

STAGE A : 11beta-[4 (methylthio)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl acid butanedioate.

1.5 g of 17beta-hydroxy-11beta-[4-(methylthio)-phenyl] 17alpha-(1-propynyl)-estra-4,9-dien-3-one, 15.3 cm^3 of chloroform are mixed in a flask provided with magnetic agitation and a cooling agent, then 1.86 g of succinic anhydride, 6 cm^3 of triethylamine and 794 mg of 4-(dimethylamino) pyridine are added and the whole is heated under reflux for 94 hours, poured into 1N hydrochloric acid and extracted with chloroform. The chloroform phase is washed with water, dried on sodium sulphate and the solvent is eliminated under reduced pressure at 40°C. 2.26 g of crude product is obtained which is chromatographed on a Kieselgel 60H ^{R} silica column (eluant : (methylene chloride 97.5 - methanol 2.5 - acetic acid 1%). After recristallisation from a methylene chloride - isopropyl ether mixture, 826 mg of crystals of the desired product are formed. M.p. = 158°C.

Rf = 0.61 (thin layer chromatography, support : KC 18 Whatman ^{R}, eluant : methanol - 0.5 molar aqueous solution of ammonium acetate (70-30).

STAGE B : Butanedioate of sodium and 11beta-[4(methylthio)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl.

The operation is carried out in the same way as in Stage B of Preparation 1 with 108 mg of sodium bicarbonate in 21.5 cm^3 of water and 719 mg of the product prepared in Stage A in 21.5 cm^3 of ethanol, 720 mg of a lyophilizate corresponding to the desired product is obtained.

$[alpha]_D$ = +74.5 ± 1.5° (c = 1% in water).

Rf = 0.61 (thin layer chromatography, support: KC 18 Whatman R, eluant : m thanol - 0.5 molar aqueous solution of ammonium acetate (70-30).

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS.

a) Injectable solutions containing 150 mg of 17beta-hydroxy-11beta-(4-dimethylaminophenyl)-17alpha-(prop-1-ynyl)-estra-4,9-dien-3-one (product A) were prepared.

b) Injectable solutions containing 300 mg of product A were prepared.

c) Injectable solutions containing 600 mg of product A were prepared.

d) Injectable solutions containing 800 mg of product A were prepared.

BIOLOGICAL TEST

The test was carried out on sows. Sows were selected according to the following criteria:

- sows of the same origin (same selection pattern),
- sows ofthe same parturition level (3rd),
- covered by the same boar or artificial insemination with semen of the same origin,
- an identical number of coverings or inseminations,
- covering or insemination on the first post-weaning heat (covering weaning interval identical or very close),
- identical sucklingduration.

The sows are divided into 3 groups of n animals:

- one control group receives no product,
- one group receives an intra-muscular injection of 2 mg/kg of product A or 17beta-hydroxy-11beta-(4-dimethylamino-phenyl)-17alpha-(prop-1-ynyl)-estra-4,9-dien-3-one, on the 113th day of gestation,
- one group receives an intra-muscular injection of 175 mcg of cloprostenol in the form of PLANATE P per sow, on the 113th day of gestation.

The time interval between the injection of the active ingredient and giving birth was measured: the following table

summaris s the results obtain d.

1. - Treated animals (Ho = 9 hours on the 113th day of gestation.

Test products	-20 H	20 to 30 H	30 to 36 H	+ 36 H
Product A	4%	92%	4%	
n = 24	1	22	1	
Cloprostenol	4.5%	78%	4.5%	13%
n = 23	1	18	1	3

2. - Control animals : simultaneous tests

	112D	113D	114D	115D	116D	117D	118D
CONTROLS	9%	13%	35%	17%	17%	4.5%	4.5%
n = 23	2	3	8	4	4	1	1

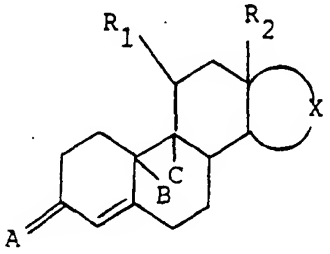
Conclusion :

The administration of product A leads to a very useful synchronization of giving birth : 92% of the animals treated give birth 20 to 30 hours after the administration of the product.

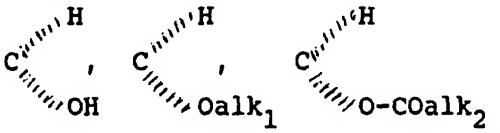
CLAIMS

1. - Use of anti-progestomimetic compounds for the manufacture of compositions intended for the synchronization of giving birth in breeding animals.

2.- Use according to claim 1, characterized in that the compounds endowed with anti-progestomimetic activity correspond to general formula (I):



(I)

in which R_1 represents a hydrocarbon radical containing 1 to 18 carbon atoms and optionally one or more identical or different heteroatoms, linked to the steroid nucleus by a carbon atom, R_2 represents a hydrocarbon radical containing 1 to 8 carbon atoms, X represents the remainder of a pentagonal or hexagonal ring optionally substituted and optionally carrying an unsaturation, the C=A group in position 3 represents a free or blocked oxo group in the form of the ketal, a  group, a C=NOH group, a $C=NOalk_3$ group or a CH_2 group, alk_1, alk_2 and alk_3 representing an alkyl radical containing 1 to 8 carbon atoms or an aralkyl group containing 7 to 15 carbon atoms and B and C together form a double bond or an epoxide bridge, as well as their addition salts with acids.

3.- Use according to claim 2, characterized in that the compounds endowed with antiprogestomimetic activity correspond to general formula (I) in which R_1 represents a hydrocarbon radical containing 1 to 18 carbon atoms containing at least one nitrogen, phosphorus or silicon atom

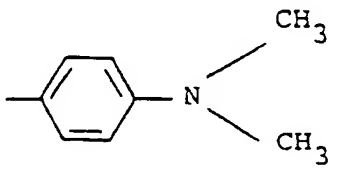
linked to the steroid nucleus by a carbon atom.

4. - Use according to claim 2 or 3, characterized in that in the product of formula (I), B and C together form a double bond.

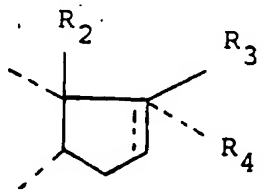
5. - Use according to any one of claims 2 to 4, characterized in that in the product of formula (I), R_2 represents a methyl radical.

6. - Use according to any one of claims 2 to 5, characterized in that in the product of formula (I), the C=A group represents a $\overset{O}{\overset{\|}{C}}$ group.

7. - Use according to any one of claims 2 to 6, characterized in that in the product of formula (I), R_1 represents a radical:

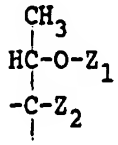


8. - Use according to any one of claims 2 to 7, characterized in that in the product of formula (I), X represents the remainder of a ring:



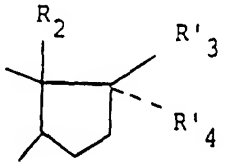
in which R_2 retains the same meaning as previously, R_3 and R_4, identical or different, represent either a hydrogen atom, or an OH, $Oalk_4$, $O\text{-}COalk_5$ radical, alk_4 and alk_5 representing an alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to 15 carbon atoms, or an alkenyl or alkynyl radical containing 2 to 8 carbon atoms, or an $-\overset{O}{\overset{\|}{C}}-CH_2OH$ radical, or a $-COCH_2OCOalk_6$ radical, in which alk_6 represents an optionally substituted alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to

15 carbon atoms, or a CO-CO_2H radical, or a CO-CO_2alk_7 radical in which alk_7 represents an alkyl radical containing 1 to 8 carbon atoms, or a $-\overset{H}{\underset{|}{C}}=O$ radical, or a $-\overset{NHalk_8}{\underset{|}{C}}=O$ radical, in which alk_8 represents an alkyl radical containing 1 to 8 carbon atoms or an aralkyl radical containing 7 to 15 carbon atoms, or a -C=N radical, or R_3 and R_4 together form a radical:



in which Z_1 represents a hydrogen atom, an alkyl radical or an acyl radical containing 1 to 8 carbon atoms and Z_2 an alkyl radical containing 1 to 8 carbon atoms.

9.- Use according to claim 8, characterized in that in the product of formula (I) X represents the remainder of a ring:



in which R_2 retains the same meaning as previously and R'_3 represents an OH radical, and R'_4 an alkynyl or alkenyl radical containing up to 4 carbon atoms.

10.- Use according to claim 9, characterized in that the anti-progestomimetic compound is 17beta-hydroxy-11beta-(4-dimethylaminophenyl)-17alpha-(prop-1- ynyl)-estra-4,9-dien-3-one.

11.- Use according to claim 9, characterized in that the anti-progestomimetic compound is (Z) 11beta-[4-(dimethylamino)-phenyl]-17beta-hydroxy-17alpha-(1-propenyl)-estra-4,9-dien-3-one.

12.- Use according to claim 9, characterized in that the anti-progestomimetic compound is 11b ta-[4-(methylthio)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl

butanedioate or one of its alkaline salts and notably its sodium salt

13.- Use according to claim 9, characterized in that the anti-progestomimetic compound is 11beta-[4-(dimethylamino)-phenyl]-3-oxo-17alpha-(1-propynyl)-estra-4,9-dien-17beta-yl butanedioate or one of its alkaline salts and notably its sodium salt.

14.- Use according to any one of claims 1 to 13, characterized in that the administration takes place in a sow.

15.- Use according to any one of claims 1 to 13, characterized in that the administration takes place in a cow.

16.- Use according to any one of claims 1 to 15, characterized in that the administration of active ingredient takes place by injection .

17.- Use according to any one of claims 1 to 14, characterized in that the product of claim 10 is administered by injection in the sow between the 109th and 114th day of gestation at a dose comprised between 1 mg and 3 mg per kg of animal weight.

18.- Use according to claim 17, characterized in that the product of claim 10 is administered in the sow by injection at a dose of 2 mg/kg of animal weight.

19.- Use as claimed in any one of the preceding claims substantially as hereinbefore described by way of Example.

DATED THIS 5th day of February, 1991

BY: TOMKINS & CO.,
Applicants' Agents

SIGNED:

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